

Pleiotropic Effects of Angiotensin Receptor Blockers: Addressing Comorbidities by Optimizing Hypertension Therapy

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The efficacy of angiotensin receptor blockers (ARBs) in the management of hypertension is well established. Whether these agents induce pleiotropic effects that promote the amelioration of vascular disorders independent of blood pressure reduction remains controversial. This review examines preclinical and clinical data that highlight a potentially important role for ARBs in several common vascular disorders, including cardiovascular, cerebrovascular, renal, and metabolic disorders. The preponderance of evidence suggests that some of the benefits derived from ARBs might improve outcomes in these disorders by actions that extend beyond blood pressure reduction. This review also identifies some potentially important differences in the mechanism of action between ARBs and angiotensin-converting enzyme inhibitors that may have clinical significance in the management of vascular diseases. J Clin Hypertens (Greenwich). 2011;13:42–51.

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Although the vascular endothelium is defined simply as the single layer of cells lining the luminal surface of blood vessels, it has a greater

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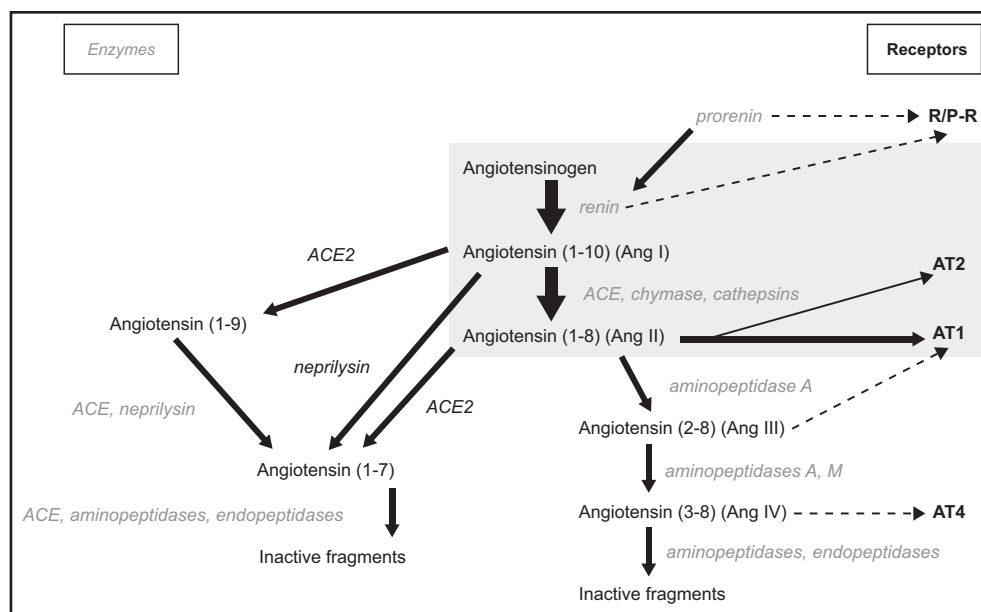
physiologic role than its definition may suggest. Endothelial cells mediate vascular dilation, inhibit the growth and proliferation of cells within the intima and media, control the flux of inflammatory white cells into the subendothelial space, and prevent thrombus formation by producing tissue plasminogen activator and prostacyclin.¹ Because of the critical role of normal endothelial functioning, it is not surprising that endothelial dysfunction is associated with a host of vascular disorders, including hypertension, atherosclerosis, type 2 diabetes mellitus, congestive heart failure (HF), and cerebrovascular disease.^{1,2} Indeed, endothelial dysfunction is now widely recognized as an antecedent condition for cardiovascular (CV) diseases.^{1,3} Under normal conditions, homeostasis and vascular tone are maintained by the proper balance of endothelium-secreted substances that promote vasodilation (eg, nitric oxide [NO], bradykinin, prostacyclin, and endothelium-derived hyperpolarizing factor) and substances that promote vasoconstriction (eg, angiotensin I [Ang I] and angiotensin II [Ang II], endothelin, thromboxane A₂, and arachidonic acid).¹ Ang II has been shown to play a key role in endothelial dysfunction, and thus may be implicated in vascular diseases beyond hypertension.³ This review will examine the pleiotropic actions of angiotensin receptor blockers (ARBs) by highlighting their metabolic and tissue-protective effects not directly attributable to blood pressure (BP) normalization.

RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAS) represents a clinically relevant enzymatic pathway that is initiated when renin hydrolyzes angiotensinogen to form the

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biologically inactive decapeptide Ang I (Figure 1).⁴ In turn, angiotensin-converting enzyme (ACE)—as well as alternative enzymes such as trypsin, cathepsin, or myocardial chymase—hydrolyze Ang I to a biologically active octapeptide, Ang II, the chief pathogenic mediator in the setting of abnormal RAS activity.⁵ At least 4 angiotensin receptor subtypes have been delineated (angiotensin type 1 [AT₁] to AT₄), with the AT₁ subtype being the main physiologic mediator for Ang II.⁵ Blockade of Ang II with ARBs that selectively target the AT₁ receptor or with ACE inhibitors that block the formation of systemic Ang II can attenuate the pathophysiologic effects of Ang II.⁵

Clinical data indicate that in the management of hypertension, ARBs provide efficacy comparable to that of ACE inhibitors but with improved tolerability.⁴ ARBs were developed to overcome some of the tolerability issues linked to the use of ACE inhibitors.^{6,7} For instance, ACE not only hydrolyzes Ang I, but also breaks down bradykinin and tachykinins such as substance P. ACE inhibition promotes the accumulation of bradykinin. Although bradykinin is beneficial in that it, too, promotes vasodilatation by augmenting NO, prostacyclin, and endothelium-derived hyperpolarizing factor production, it has been implicated in the development of treatment-limiting side effects such as dry cough and, in some patients, angioedema.⁸⁻¹⁰ ARBs exert no effect on bradykinin or substance P levels and are associated with a lower incidence of cough compared with ACE inhibitor therapy.^{7,11}

BEYOND BP CONTROL: PLEIOTROPIC ACTION OF ARBS

CV and renal disease can be viewed as part of a continuum that begins with exposure to traditional risk factors such as hypertension, dyslipidemia, insulin resistance, and obesity that trigger or amplify endothelial dysfunction and ultimately progress to end-organ damage (Figure 2).¹² In this scenario, Ang II exerts a critical influence in all phases of disease development by spurring endothelial cell dysfunction, and, in turn, vascular wall remodeling, atherosclerosis, left ventricular hypertrophy (LVH), and glomerulopathy, among other effects.^{13,14} In recent years, many preclinical and clinical trials have attempted to identify the mechanism and the extent of the pleiotropic actions of Ang II blockers such as ARBs.

CORONARY ARTERY DISEASE

Preclinical Findings

In coronary artery disease, macrophages can amplify maladaptive inflammatory and thrombogenic processes through the accumulation of oxidatively modified low-density lipoprotein (LDL) that results in the formation of foam cells, a key histologic substrate of atherogenesis.¹⁵ Peroxisome proliferator-activated receptor γ (PPAR- γ) is a nuclear transcription factor that plays an important role in lipid and glucose metabolism, as well as in the inflammatory response.¹⁵ In vivo, PPAR- γ agonists inhibit the formation of macrophage foam cells, decrease the rate

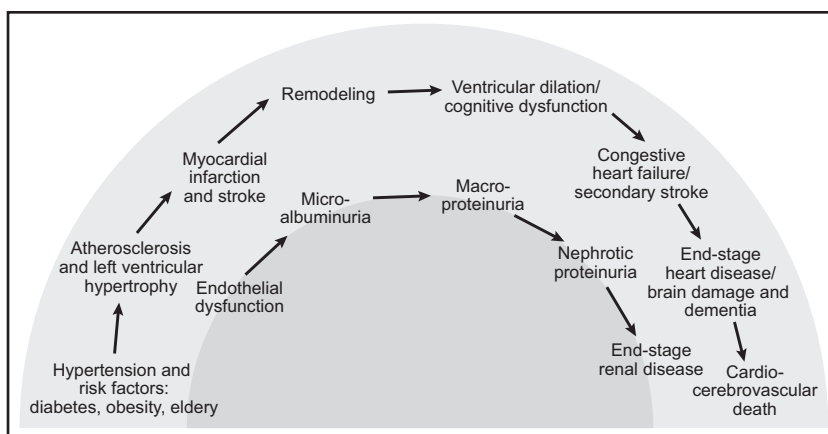


Figure 2. The cardiovascular-renal continuum. Adapted with permission from Ruilope et al.¹²

of cholesterol esterification, and augment cholesterol efflux from macrophages, suggesting an important beneficial modulatory effect on cholesterol homeostasis and atheromatous lesion formation.¹⁵ In vitro, telmisartan, candesartan, irbesartan, and losartan—but not valsartan or olmesartan—are PPAR- γ ligands.^{16,17} Other investigations have shown that ACE inhibitors such as lisinopril also display PPAR- γ agonism, although the ARB telmisartan displayed a greater affinity in that study.¹⁸

In addition to their agonism of PPAR- γ , ARBs may influence other endothelial factors involved in atherogenesis. In a study that included 60 apolipoprotein E-deficient mice with advanced atherosclerotic lesions, reductions in the progression of atherosclerotic lesion size were noted in 38% and 18%, respectively, with telmisartan or ramipril treatment compared with placebo.¹⁹ Immunohistochemical analysis revealed that telmisartan-treated mice displayed reduced macrophage content in atherosclerotic lesions compared with ramipril-treated mice. The investigators attributed the reduction in atherosclerotic disease progression with telmisartan vs ramipril to reduced activity of proinflammatory transcription factors nuclear factor κ B and early growth response gene-1 and the increased activation of PPAR- γ .

Biglycan has emerged as another potentially important mediator of atherosclerosis. A build up of biglycan (a small, leucine-rich proteoglycan) in the intima fosters the retention and trapping of lipids and the formation of macrophage foam cells during the early stages of atherogenesis.²⁰ Biglycan levels increase in response to the presence of oxidized lipids, interleukin 1, tissue growth factor β -1, and Ang II. In a recent 12-week study in apolipoprotein E-deficient mice, a model of accelerated atherosclerosis, biglycan accumulation was reduced

by treatment with the ARB telmisartan, but not by the smooth muscle relaxant hydralazine.²⁰

Clinical Findings

Several major well-controlled clinical trials (Swedish Irbesartan Left Ventricular Hypertrophy Investigation vs Atenolol [SILVHIA],²¹ Losartan Intervention for Endpoint Reduction in Hypertension [LIFE],²² and Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET]²³) suggest that ARBs can confer CV benefits beyond reductions in BP in patients without HF, and these benefits appear similar to those seen with the use of ACE inhibitors. During these trials, study drug adjustments and the use of other antihypertensive agents were permitted to normalize BP.

In the SILVHIA study, 115 patients with hypertension and LVH were treated either with daily irbesartan (150 mg) or daily atenolol (50 mg) for 48 weeks.²¹ By study's end, BP reductions were equivalent in both groups; however, significantly greater reductions in left ventricular mass were observed with irbesartan (16%) vs atenolol (9%). Moreover, a greater percentage of patients achieved normal left ventricular mass with irbesartan (47%) than with atenolol (32%), although this difference did not reach statistical significance. These results imply that in patients without HF, the use of ARBs may be a more effective strategy for mitigating LVH than β -adrenergic blockade. In addition, in the large long-term LIFE trial, which included 9193 patients with hypertension and LVH who were treated with either a losartan-based or an atenolol-based regimen for at least 4 years (mean of 4.8 years), ARB therapy provided CV benefits that apparently extended beyond that of BP reduction.²² In the subgroup with LVH on screening

electrocardiography, patients receiving the losartan-based regimen had greater LVH regression than those treated with the atenolol-based regimen.²⁴ As in the SILVHIA study, BP reductions were similar for both regimens, yet the primary CV end point—death, myocardial infarction (MI), or stroke—occurred significantly less frequently with the ARB-based therapy, with a relative risk reduction for this end point of 13% vs atenolol.

Whether ARBs offer cardioprotective effects similar to those achieved with ACE inhibitors remains controversial, with some investigators suggesting that ARB treatment may enhance the risk for MI in high-risk patients with coronary, peripheral, or cerebrovascular disease.^{25,26} Results from the ONTARGET trial helped clarify the cardioprotective role of ARBs vis-à-vis ACE inhibitors.²³ This long-term (median follow-up of 56 months) study included more than 25,000 patients without HF who had uncontrolled hypertension while on treatment (>160/100 mm Hg) and coronary, peripheral, or cerebrovascular disease or diabetes mellitus with end-organ damage and who were treated with either ramipril 10 mg or telmisartan 80 mg, or a combination of both agents.²³ During the study, BP was only slightly lower in the telmisartan and combination therapy groups than in the ramipril group. The primary outcome—death from CV causes, MI, stroke, or hospitalization for HF—occurred at similar rates in the ramipril (16.5%) and telmisartan (16.7%) groups; combination therapy offered no advantages. In addition, CV mortality, MI, or stroke, the secondary end point, was similar with telmisartan (13.9%) and ramipril (14.1%) treatment. The incidences of cough and angioedema leading to study discontinuation were significantly lower with telmisartan (1.1% and 0.1%, respectively) vs ramipril (4.2% and 0.3%, respectively)²⁷; this is quite impressive considering the fact that the patients were evaluated early on during a run-in period for their ability to tolerate ACE inhibitor therapy.

HEART FAILURE

Preclinical Findings

A part of the pathophysiology of HF has been linked to impairments in NO-mediated vasodilation, resulting from a reduction in the expression of the leucine zipper positive (LZ⁺) isoform of the myosin-targeting subunit (MYPT1) of myosin light-chain phosphatase, which modulates the interaction between actin and myosin.²⁸ In the 2- to 4-week period following an MI, expression of LZ⁺ MYPT1 and arterial sensitivity to NO decrease. In a study in rats with left anterior descending artery ligation (LADAL), a

model of MI in rodents, losartan administration after ligation maintained LZ⁺ MYPT1 expression and decreased the activation of the p42/44 mitogen-activated protein kinase (MAPK) cascade, a pathway activated in animal models of HF and involved in cardiac remodeling.^{29,30} These findings were consistent with those previously demonstrated with captopril.^{29,31} These findings suggest that ARBs and ACE inhibitors may confer beneficial action in HF by blocking Ang II-mediated reductions in LZ⁺ MYPT1 and increases in p42/44 MAPK signaling.

Another study in rats that had undergone LADAL demonstrated that short-term (2 or 6 weeks) ARB therapy with candesartan after the development of post-MI left ventricular remodeling significantly reduced monocyte chemoattractant protein-1 (MCP-1) expression (an important mediator of LVH immediately after an MI), monocyte infiltration, and ultimately myocardial fibrosis in infarct border-zone regions.³² In this study, ARB administration resulted in reduced inflammation, tissue injury, and fibrosis development in the border zone.

Endothelial progenitor cells (EPCs) are derived from bone marrow. EPCs differentiate into endothelial cells, participate in the neovascularization of tissue damaged by ischemia, and display the ability to repair damaged CV tissue.³³ Oxidative stress results from the production of oxygen-free radicals such as superoxide anion, hydroxyl radicals, and peroxynitrite. These species are potent oxidizing agents and induce cell toxicity and tissue injury. EPC dysfunction has been linked to vascular injuries secondary to Ang II-driven oxidative stress, such as that triggered by hypertension, diabetes mellitus, and smoking. Oxidative stress can also shorten the lifespan of cardiac stem cells (CSCs), which are thought to be important in the regeneration of damaged cardiac tissue. In a study that included 24 salt-loaded, spontaneously hypertensive rats that were treated with candesartan, a diuretic (trichloromethiazide), or an antioxidant (tempol), or were untreated for 2 weeks, candesartan suppressed Ang II-induced oxidative stress and improved EPC and CSC function, suggesting an Ang II blocker-related improvement in endothelial function that may be valuable in HF management.³³ In addition, other investigators have shown that EPCs obtained from healthy human volunteers underwent an increase in number and function when exposed to telmisartan, an action attributed to PPAR- γ activation.³⁴

Clinical Findings

The Valsartan in Acute Myocardial Infarction (VALIANT) trial included almost 15,000 patients

who had experienced a recent MI complicated by clinical or radiologic signs of HF, left ventricular systolic dysfunction, or both who were treated with valsartan, valsartan plus captopril, or captopril alone.³⁵ The ARB valsartan (titrated to 160 mg twice daily) was as effective as the ACE inhibitor captopril (titrated to 50 mg 3 times daily) in reducing all-cause death after a 2-year follow-up. No significant differences were seen among groups in systolic or diastolic BP. With combined captopril/valsartan therapy (titrated to 50-mg captopril 3 times daily/80-mg valsartan twice daily), no additional therapeutic benefit was achieved and the risk for adverse events increased. Dose reductions owing to cough occurred less frequently with valsartan (1.7%) vs captopril (5.0%); however, dose reductions prompted by hypotension or increased serum creatinine levels were higher with valsartan (15.1% and 4.9%, respectively) than with captopril treatment (11.9% and 3.0%, respectively). These findings support the conclusion that valsartan 160 mg twice daily is as effective as captopril 50 mg 3 times daily in increasing survival in patients with HF.

RENAL DISEASE

Preclinical Findings

Endothelin-1 (ET-1), a potent endothelial growth-promoting and vasoconstrictor peptide, has been shown to play a central role in promoting proteinuria, a marker for renal injury, and glomerulosclerosis.³⁶ ET-1 production can be enhanced by a variety of factors, including Ang II, aldosterone, reactive oxygen species, hypertension, and inflammation. ET-1-binding sites are present in podocytes, structural cells that line the glomerular filtration barrier, and Ang II, which induces renal ET-1 synthesis, can foster podocyte disruption and, in turn, glomerulosclerosis. In rats with experimentally induced microalbuminuria, which display pathologic features of renal injury similar to that seen in humans, the administration of telmisartan for 22 weeks yielded significant declines in intrarenal Ang II levels and markers for podocyte injury compared with hydralazine or placebo administration.³⁷ These findings imply that Ang II blockade could slow the transition from microalbuminuria to overt nephropathy independent of changes in BP by blocking the growth-promoting and vasoconstricting actions of intrarenal Ang II, perhaps through the attenuation of ET-1 synthesis.

A study using cultured mouse tissue investigated how Ang II inhibition affects the interaction between podocytes and glomerular endothelial cells.³⁸ Super-

natant from normal mouse podocytes enhanced the sprouting of glomerular endothelial cells, whereas supernatant from mice with injured podocytes decreased it. This effect was associated with vascular endothelial growth factor A and angiopoietin-1 downregulation in the injured podocytes, a process that was reversed with administration of the ARB losartan. Thus, losartan may have the capacity to restore the sprouting of glomerular endothelial cells, capillary remodeling, and inhibition of renal disease progression independent of BP reduction.

Clinical Findings

Although antihypertensive therapy generally slows the progression of renal dysfunction, accumulating evidence suggests that both diabetic and nondiabetic renal disease may be especially responsive to agents that block Ang II.³⁹ Major clinical trials such as the Irbesartan in Diabetic Nephropathy Trial (IDNT),⁴⁰ Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL),⁴¹ Irbesartan Microalbuminuria II trial (IRMA II),⁴² and Microalbuminuria Reduction With Valsartan (MARVAL)⁴³ studies have explored the effects of Ang II blockers in the management of renal disease.

In IDNT, 1715 hypertensive patients with diabetic nephropathy received treatment with irbesartan 300 mg, amlodipine 10 mg, or placebo for an average of 2.6 years.⁴⁰ Although both active treatments yielded reductions in BP that were statistically greater than those achieved with placebo, no differences were seen between the active treatment groups. The incidence of the primary end point—a composite of doubling of baseline serum creatinine concentration, development of end-stage renal disease, or all-cause mortality—was significantly reduced with ARB treatment compared with placebo (20%) or amlodipine (23%) treatment. Moreover, with irbesartan treatment, the risk of doubling serum creatinine concentrations was significantly reduced (33% and 37%) vs placebo and amlodipine, respectively. The risk for end-stage renal disease also declined with irbesartan, but the 23% reduction seen vs that obtained with amlodipine or placebo did not achieve statistical significance.

The RENAAL trial also supports the use of an ARB in the setting of diabetic nephropathy.⁴¹ This study included 1513 hypertensive patients with diabetic nephropathy who were randomized to treatment with either losartan (50–100 mg) daily or placebo for an average of 3.4 years. Despite similar between-group BP reductions, losartan treatment reduced the risk of reaching the primary end point (composite of a doubling of the baseline serum

creatinine concentration, end-stage renal disease, or death) by a significant 16%, and it reduced the risks of doubling of baseline serum creatinine and of end-stage renal disease by a significant 25% and 28%, respectively, compared with placebo.

The IRMA II trial included 590 patients with type 2 diabetes and hypertension but with less severe renal disease (persistent microalbuminuria) than patients in IDNT and RENAAL.⁴² In this 2-year study, patients received irbesartan 150 mg or 300 mg or placebo. Throughout the study, little variation was noted in absolute BP readings among groups. During the study, the development of diabetic nephropathy (primary end point)—defined as persistent albuminuria, with a urinary albumin excretion rate >200 µg/min and 30% higher than baseline—was reached by 5.2%, 9.7%, and 14.9% of patients treated with irbesartan 300 mg, 150 mg, or placebo, respectively. Compared with placebo treatment, significant reductions in the risk for diabetic nephropathy emerged for irbesartan 150 mg (39%) and 300 mg (70%). Irbesartan 150 mg and 300 mg also yielded significant dose-dependent reductions in urinary albumin excretion levels of 24% and 38%, respectively. In this study, irbesartan appeared to exert dose-dependent renal benefits in hypertensive diabetic patients independent of BP reductions.

The 24-week MARVAL trial compared daily doses of the ARB valsartan (80 mg) with the calcium channel blocker (CCB) amlodipine (5 mg) in normotensive and hypertensive patients with diabetes mellitus and persistent microalbuminuria.⁴³ Compared with amlodipine treatment, valsartan yielded significant reductions in the primary end point—change in urinary albumin excretion rate (UAER) from baseline to week 24. Valsartan treatment also resulted in a progressive decline in UAER, culminating in a 44% decrease at week 24, compared with an 8% decline for amlodipine. In addition, significantly more patients reverted to normoalbuminuria with valsartan (29.9%) vs amlodipine (15%). These results suggest that valsartan 80 mg mitigates UAER more effectively than amlodipine 5 mg and that this beneficial effect is, to some degree, independent of BP reductions. Other studies have shown that in the mitigation of diabetic nephropathy, the efficacy of ARBs is similar to that of ACE inhibitors.^{44,45}

CEREBROVASCULAR DISEASE

Preclinical Findings

Animal studies indicate that Ang II can exert a critical influence in stroke development.⁴⁶ In a study

that included 29 rats that underwent ET-1–induced middle cerebral artery occlusion, a model that closely resembles embolic stroke, the systemic administration of candesartan during a 7-day period before experimental occlusion reduced infarct size and neurologic deficits compared with control animals without affecting BP.⁴⁶ Other investigators have shown that in rats with experimentally induced middle cerebral artery occlusion, the oral administration of the ARB telmisartan (1 mg/kg) for 7 days before the experimental procedure also yielded significant reductions in infarct volume compared with lower-dose losartan (0.25 and 0.50 mg/kg) and vehicle.⁴⁷ In addition, ARB treatment mitigated sensorimotor stroke symptoms and reduced the expression of the neurotoxic protein cytosolic phospholipase A₂. These findings provide intriguing preclinical evidence suggesting that ARBs such as telmisartan may convey a neuroprotective effect by inhibiting the signaling of cytosolic phospholipase A₂.

Another study in rats specifically investigated chronic AT₁ receptor blockade on cerebral microvascular growth.⁴⁸ Vessel density in brain sections was evaluated after up to 14 days of treatment with losartan or vehicle. Since losartan lowered BP relative to vehicle, captopril and captopril plus furosemide were added as active controls to achieve the same BP reductions as losartan. Animal brains were subsequently sectioned and microvessel density was measured. Cerebral vessel density, indicative of cerebral angiogenesis, increased significantly in the groups treated with losartan (both the 3-day and 14-day treatment groups) compared with vehicle, while no significant change was observed in the animals treated with captopril or captopril plus furosemide compared with vehicle alone, despite reductions in BP similar to those achieved with losartan in the active control groups. The authors concluded that the findings unmasked an unexpected effect of losartan administration not seen with captopril that illuminated a possible mechanism for the stroke-protective actions of AT₁ receptor blockade.

Clinical Findings

The Study on Cognition and Prognosis in the Elderly (SCOPE) study examined whether the ARB candesartan reduces the risk for stroke in the elderly with isolated hypertension.⁴⁹ This 48-month, randomized, double-blind study included nearly 5000 patients older than 70 years who were treated with once-daily candesartan (8–16 mg) or placebo. Background antihypertensive medications other than ARBs were

permitted to achieve BP normalization. During the study, both treatments reduced BP, although the difference between groups was not statistically significant. The primary end point—occurrence of first major CV event defined as CV death, nonfatal MI, or nonfatal stroke—was reduced by a nonstatistically significant 11% with candesartan vs placebo treatment. However, the relative risk for first stroke, either fatal or nonfatal, was lowered by a significant 42% with candesartan treatment. The authors concluded that the favorable results observed with regard to stroke with candesartan may be related more directly to AT₁ receptor blockade itself, independent of BP normalization.

A separate large randomized clinical study (Prevention Regimen for Effectively Avoiding Second Strokes [PROFESS] trial) examined the neuroprotective effects of antiplatelet agents and the ARB telmisartan in approximately 20,000 patients who had recurrent strokes.⁵⁰ Patients received treatment with either aspirin 25 mg and extended-release dipyridamole 200 mg twice daily or clopidogrel 75 mg once daily and either telmisartan 80 mg or placebo once daily for an average follow-up period of 2.4 years. The findings revealed no clinically meaningful differences among the treatments. Recurrent strokes occurred in 9% of the patients in each treatment group, and no differences were noted among groups in measures of mental functioning, dementia, or disability after recurrent stroke. Taken together, these studies imply that ARBs may provide their greatest benefit in cerebrovascular disease as a step in primary, but not secondary, prevention.

METABOLIC DISEASE

Preclinical Findings

Adipose tissue is no longer considered just a simple energy storage organ, but an endocrine organ that secretes adipocytokines, proteins that exert an autocrine, paracrine, or endocrine action with numerous metabolic functions. Adipocytokines include proteins relevant to insulin resistance such as adiponectin, angiotensinogen, resistin, tumor necrosis factor α (TNF- α), interleukin 6, and plasminogen activator inhibitor-1.⁵¹ Kurata and colleagues⁵² investigated the effects of the ARB olmesartan on the dysregulation of adipocytokines in genetically and diet-induced obese mice. Olmesartan blocked reduction in adiponectin, a hormone that promotes insulin sensitivity without affecting body weight.^{51,52} In addition, olmesartan normalized the regulation of adipocytokines associated with obesity, such as TNF- α and plasminogen activator inhibitor-1

(PAI-1). In culture, olmesartan also acted as an antioxidant by attenuating the mRNA elevation of PAI-1 and MCP-1 in H₂O₂-treated adipocytes. A study using a rat model of type 2 diabetes examined whether treatment with an AT₁ receptor antagonist (LI58809) for 6 months would improve insulin resistance in these animals by modulating adipose tissue function.⁵³ Treatment with LI58809 improved insulin resistance in these animals, assessed by an intraperitoneal glucose tolerance test, and markedly attenuated AT₁-mediated oxidative stress and increased adiponectin and PPAR- γ levels. These preclinical studies suggest that ARB treatment may mitigate metabolic disorders by inducing beneficial modifications in adipose tissue.

Other investigators have shown that exposure of human umbilical vein endothelial cells to Ang II resulted in inhibition of insulin-stimulated production of NO.⁵⁴ Insulin promotes a vasodilatory effect by activating the insulin receptor/insulin receptor substrate-1 (IRS-1) phosphatidylinositol 3-kinase/Akt pathway that stimulates endothelial NO synthase and, in turn, NO levels. Ang II interferes with insulin-induced tyrosine phosphorylation of IRS-1, thereby interfering with insulin signaling. Administration of the ARB losartan blocked the Ang II inhibition of insulin signaling. The mitigation of Ang II-induced insulin resistance in the endothelium by losartan provides another possible mechanism by which these agents may reduce the risk for type 2 diabetes, independent of BP reduction.

Clinical Findings

The results of the recently published Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study examined the role of ARBs on the risk for new-onset type 2 diabetes.⁵⁵ This double-blind, randomized, 5-year trial included 9306 patients with impaired glucose tolerance and established CV disease or CV risk factors treated daily with the ARB valsartan (up to 160 mg) or placebo. All patients underwent lifestyle changes that were designed to reduce the risk for diabetes, such as achieving and sustaining a 5% weight loss, reducing intake of saturated fat, and increasing physical activity to 150 minutes per week. During the study, patients were permitted to take background antihypertensive, lipid-lowering, and antiplatelet treatments. The patients in this trial had well controlled BP. Compared with placebo, valsartan treatment yielded a significant relative reduction of 14% in the risk for new-onset type 2 diabetes, with an incidence of 33.1% and 36.8% in the valsartan and placebo groups, respectively. The

authors estimated that valsartan therapy in this type of population could prevent 38 cases of new-onset diabetes per 1000 patients treated over 5 years.

A randomized 3-month study that included 65 patients with impaired fasting glucose and/or glucose intolerance compared the effects of the ARB losartan (25–100 mg) with a CCB such as amlodipine, azelnidipine, cilnidipine, or benidipine on high-molecular weight adiponectin levels and insulin sensitivity.⁵⁶ Despite similar BP reductions between groups, losartan treatment produced significant elevations in adiponectin concentrations (45.9%), along with significant improvements in insulin sensitivity, compared with CCB treatment. These results suggest that losartan may mitigate type 2 diabetes independent of BP reductions by elevating serum adiponectin levels. Moreover, in a 20-month randomized study that included 54 patients with nonalcoholic steatohepatitis and mild to moderate hypertension, daily treatment with telmisartan 20 mg resulted in greater improvements in ALT values and insulin resistance compared with valsartan 80-mg treatment, despite similar changes in BP for both groups.⁵⁷ Because telmisartan significantly decreased the nonalcoholic steatohepatitis score and fibrosis score compared with valsartan, the authors suggested that telmisartan's principal mechanisms of action involved both AT₁ receptor blockade and PPAR- γ modulation.

In the large and long-term (>4 years follow-up) LIFE and Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trials, the incidence of new-onset type 2 diabetes was reduced by 25% and 20%, respectively, when ARB-based treatment was compared with either β -blocker- or CCB-based regimens.^{22,26} In these trials, BP reductions were similar for the ARB and comparator groups. Furthermore, the results of a meta-analysis that examined the role of Ang II blockade on the development of type 2 diabetes found that ARBs and ACE inhibitors, as a class, convey a consistent reduction in risk for type 2 diabetes.⁵⁸

CONCLUSIONS

Previous outcome studies show that ARBs lower BP as effectively as ACE inhibitors, with fewer adverse events. Recent molecular, histologic, and clinical data also suggest that the ARBs confer additional benefits not attributable to BP normalization—or even RAS axis inhibition—alone. Although the molecular complexities that underlie the pleiotropic effects of these agents remain to be clearly elucidated, at least some are directly related

to the amelioration of abnormalities in endothelial cell function common in vascular disease states, including coronary artery disease, stroke, and metabolic disorders. Whether the pleiotropic benefits of ARBs on insulin resistance and coronary artery disease are mediated by extra-RAS effects such as PPAR- γ agonism, regulation of adipocytokine expression, maintenance of normal insulin receptor signaling, and beneficial effects on the biochemical and histologic organization of vessel walls remains an intriguing but yet-to-be established proposal. There is, however, growing experimental and clinical support for such roles.

Abnormalities in the RAS and in endothelial function in vascular diseases appear intimately related. A growing body of clinical trial evidence highlights an important role for RAS axis modulation in improving outcomes in patients with CV, cerebrovascular, renal, and metabolic disorders. Their place in patient care is well established in clinical guidelines. Whether therapy with ARBs and ACE inhibitors convey similar beneficial pleiotropic actions remains a subject that is evolving and controversial. At the least, the preponderance of clinical evidence suggests that these agents offer comparable protection against CV and renal disease progression, independent of BP normalization. ARBs, however, are typically associated with fewer troublesome side effects such as dry cough, which makes these agents appealing alternatives to ACE inhibitors in the clinical setting. The pathophysiology of CV and renal disease is enormously complex. It is possible that in order to more firmly establish the clinical relevance of pleiotropic effects, treatment for far longer periods than is feasible in clinical trials would be required, since reversing or healing chronic injury is a process that likely requires long periods.

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